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DEBATE—continued

What is the most relevant standard of success in assisted reproduction?

The cumulated singleton/twin delivery rates per oocyte pick-up: the CUSIDERA and CUTWIDERA

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National and international registries are essential tools for establishing new standards and comparing success rates, but they do not take into account the total pregnancy/delivery rate per oocyte recovery. In Switzerland and Germany, because of legal constraints, a maximum of three two-pronuclear zygotes are allocated for transfer whereas all the supernumerary pronuclear zygotes are immediately cryopreserved, preventing selection of the transferred embryos. We report on a 10 years' experience (1993–2002) of our centre which performs transfers of unselected embryos and cryopreservation at the two-pronuclear zygote stage. As ~30% of all deliveries are from cryo cycles, it is essential to take into account the contribution of the cryo transfers, and we propose therefore to evaluate, as a measure of IVF performance, the cumulated delivery rate per oocyte pick-up. This delivery rate is broken down further into the cumulated singleton delivery rate (CUSIDERA) and the cumulated twin delivery rate (CUTWIDERA). The sum (S) of these two rates is a measure of efficacy while the ratio CUTWIDERA/S as a percentage is a measure of safety of IVF treatments. Using these new indexes, the average 10 year efficacy and safety of our IVF programme were 26 and 19%, respectively. Both CUSIDERA and CUTWIDERA can be calculated easily in any clinical situation and yield useful parameters for patient counselling and internal/external benchmarking purposes.

Key words: cryopreservation/cumulated delivery rates/IVF/multiple pregnancies/treatment efficacy

Introduction

The outcome measure of an IVF treatment has been critically reviewed in several recent issues of this journal (Davies *et al.*, 2004; Dickey *et al.*, 2004; Griesinger *et al.*, 2004; Land and Evers, 2004; Min *et al.*, 2004). The debate has focused not only on the clinical performance in terms of pregnancy or delivery rates per any type of denominator, but also on other associated risks and complications, such as multiple births or other maternal risks. The safest approach to assisted reproduction has been proposed to be 'Children for infertile couples, but one at a time' (Adashi *et al.*, 2003). Reducing the number of transferred embryos from three to two has been shown in several studies to reduce the multiple gestation rates without affecting the pregnancy rate per transfer (Staessen *et al.*, 1995; Templeton and Morris, 1998). Along the same line of thought, the transfer of a single embryo has become a legal obligation in some countries with the objective of reducing the twin pregnancy rate (Gerris *et al.*, 2002; Adashi *et al.*, 2003). Elective single embryo transfer (eSET) is, however, technically dependent on an *in vitro* selection of the most suitable embryo (Martikainen *et al.*, 2004), which is impossible to apply in some countries for legal reasons.

In Switzerland and Germany, the law restricts to three the number of embryos that may be kept in culture beyond the two-pronuclear (2PN) zygote stage (Germond and Senn, 1999; van der Ven *et al.*, 2002). Furthermore, as cryopreservation of the second or third best cleavage stage embryo is forbidden, the transfer of a single embryo would imply the destruction of the non-transferred ones. eSET is thus in our context legally and ethically inapplicable. The remaining choices are to keep only two zygotes in culture and cryopreserve all supernumerary 2PN zygotes. The consequences of this attitude are a lower pregnancy rate per transfer compared with that obtained after the transfer of selected embryos and the necessity to establish a high standard cyropreservation programme at the 2PN zygote stage.

Cryopreservation has to be considered in evaluating IVF outcome

Most centres evaluate their IVF performance by measuring pregnancies or deliveries following fresh embryo transfers without including cryo transfers. Cumulating fresh and cryo transfers has been presented recently as a critical issue to

evaluate outcome of IVF treatments (Davies *et al.*, 2004; Pinborg *et al.*, 2004). In the Swiss and German context, it is essential to take into account the contribution of the cryo transfers, and we propose therefore to evaluate, as a measure of IVF performance, the cumulated delivery rates per oocyte pick-up (OPU). This measure can be broken down further into the cumulated singleton delivery rate (CUSIDERA) and the cumulated twin delivery rate (CUTWIDERA), as shown in Figure 1.

When only fresh transfers were considered, the singleton delivery rate per OPU obtained in our centre reached 13.1%, which was similar to the birth emphasizing successful singleton at term (BESST, 11.1%) reported by Min *et al.* (2004). However, when the corresponding frozen transfers were included, the CUSIDERA increased to 21.7%. The CUSIDERA increased over the years and has reached values close to 25% since 1998. The lower rate observed for the year 2002 is due to the fact that most zygotes frozen in 2002 have not been thawed and transferred yet. When calculated according to age at the time of OPU, both CUSIDERA and CUTWIDERA decreased with age (<35 years: 26.6 and 6.2%, 35–39 years: 19.9 and 5.0%, >39 years: 9.3 and 1.5%).

Policies concerning selection and cryopreservation of human embryos vary among different countries, mainly due to specific local ethical considerations and legal constraints. One of the main advantages of CUSIDERA and CUTWIDERA is that they may be used to evaluate outcomes independently of the freezing policy and the cleavage stage of the embryos at freezing. This may allow the strategy resulting in the best outcome to be determined. The benefits of freezing zygotes instead of embryos were already demonstrated (Senn *et al.*, 2000), but a recent report on the improvement of blastocyst freezing (Gardner *et al.*, 2003) is also promising.

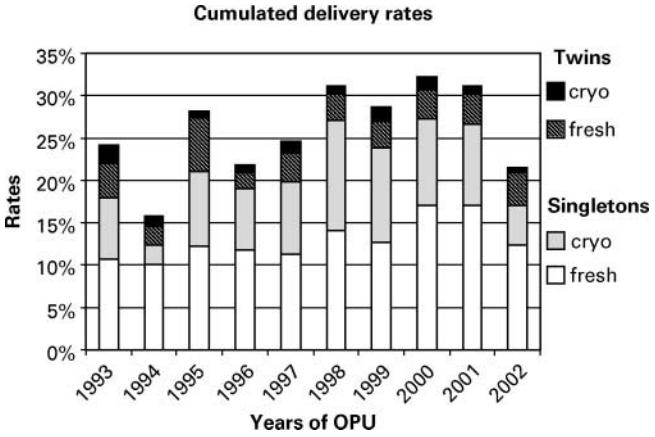

Figure 1. Cumulated singleton and twin delivery rates according to the year of OPU. The cumulated rates were calculated as the number of deliveries resulting from fresh and cryo transfers per OPU. Stimulated IVF/ICSI cycles ($n = 4122$) performed in our centre from January 1993 to December 2002 were extracted from the Swiss national FIVNAT-CH registry. Up to three 2PN zygotes were allocated for fresh transfer, while all supernumerary zygotes were immediately frozen using a slow freezing technique. Each frozen straw contained one or two zygotes in order to thaw the exact number of zygotes which had been determined previously during patient counselling. Thawed zygotes were cultivated for 24 h before the transfer, to allow for the first cleavages to occur.

CUTWIDERA and CUSIDERA as a measure of safety and efficacy

The sum of CUSIDERA and CUTWIDERA may be used as a measure of efficacy, and the ratio of CUTWIDERA/(CUSIDERA + CUTWIDERA) × 100 may be considered as a measure of safety. This safety ratio is 19% [(5/(21 + 5)) × 100] in our centre. In order to approach the natural twin conception of 1–2% (Antoine *et al.*, 2004), the CUTWIDERA should be lowered to at least 1%, but this should be achieved without affecting the CUSIDERA.

Land and Evers (2004) compared efficacy (delivery rate per OPU) related to safety (number of embryos per transfer) between different countries. In their study, Switzerland, when only fresh transfers were included, presented a low efficacy ($<20\%$ delivery rate per OPU) combined with a high safety (≤ 2 embryos per transfer). By determining efficacy with the CUSIDERA and CUTWIDERA, Switzerland would have appeared in the quadrant which combines both maximum efficacy and safety (26% efficacy with two transferred embryos), despite the lack of embryo selection. In our opinion, this increase in efficacy is due to the use of the 2PN zygote freezing policy, which maximizes the recovery of intact zygotes after thawing and minimizes the number of discarded embryos.

Twin deliveries should be reduced

Triplet pregnancies can be nearly eliminated by limiting the number of transferred embryos to two. Reducing the number of twin pregnancies is still a matter of debate, as the birth of twins may appear acceptable for a number of patients and clinicians (Dickey *et al.*, 2004). However, twin pregnancies are more likely to be responsible for premature birth and growth retardation than single pregnancies, resulting in a costly medical follow-up during gestation, the perinatal period and childhood (Adashi *et al.*, 2003). In addition, the economic and psychological difficulties of parents after the birth of twins cannot be denied. To reduce twin pregnancies, the transfer of a single embryo is the only efficient policy. However, in order to avoid a drop in the outcome, eSET implies an accurate selection of the best embryo, combined with great expertise in clinical and laboratory work (Gerris *et al.*, 2002).

Under the pressure of neonatologists, the Swiss Reproductive Medicine Society has strongly encouraged centres since 1998 to reduce the number of transferred embryos to two. This change has not compromised the pregnancy outcome in our centre and had little impact on the CUTWIDERA, which remained close to 5% over the last 10 years. As a consequence, to reach a 1% CUTWIDERA, better selection tools at the patient, zygote and oocyte levels need to be developed.

Conclusion

The combined use of CUSIDERA and CUTWIDERA should satisfy quality assurance by allowing a standardized evaluation of both efficacy and safety and by offering a benchmarking tool for internal/external audits. CUSIDERA

and CUTWIDERA may be calculated in all clinical situations and allow counselling of patients more specifically and comparison of centres or countries in terms of efficacy/safety. Finally, this measure may also prove to be the most relevant standard of success when ethical and legal arguments or public health costs are considered.

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